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10/520,693	01/20/2006	Alastair Dixon	GJE-7135	9643

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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,693	DIXON ET AL.	
	Examiner	Art Unit	
	Samuel Woolwine	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/28/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitations "the FAP" and "the primer sequences FAP and TAP" in steps (i) and (ii) respectively. There is insufficient antecedent basis for this limitation in the claim. It is not clear what "the FAP" and "the primer sequences FAP and TAP" refer to. It will only be assumed for purposes of further examination that the recited heeled 5'-amplification primer comprises a variable sequence. Similarly, it will only be assumed that the heeled primers comprise primer binding sites to which the "primers sufficiently complementary" in step (ii) of claim 1 can bind. Applicant is advised to amend the claims to make clear what components each of the heeled primers comprises and in the case that one component is found within another, what the relationships among the components are.

Claims 2-18 are dependent on claim 1 and are rejected for the same reasons.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 and 8-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Richardson et al (WO 01/06004 A2, cited on the IDS of 8/28/2006).

With regard to claim 1, Richardson teaches a *method for increasing the number of polynucleotides containing sequences corresponding to a mRNA species present in a sample* (e.g. page 25, lines 27-29), *the method comprising the steps of:*

(i) reverse transcribing the mRNA species using a heeled 5'-amplification primer (FAP-RAND) (e.g. "first heeled primer population"; page 25, lines 30-31)

and a heeled 3'-amplification primer (TAP-RT) (e.g. "second heeled primer population"; page 25, lines 32-33),

wherein each primer sequence is unique (it is noted in paragraph [0007] of Applicant's published application: "[a]nother advantage is that the production of complex products is minimised, due in part to the use of unique sequences in FAP and TAP which are absent from the genome being investigated"; however, Richardson clearly teaches this concept in, for instance, Example V, pages 55-58, wherein the primer sequences were chosen based on their absence from the genome being investigated (see page 55, lines 29-30 and page 56, lines 25-26; also note that Richardson teaches that the heel sequence of the first heeled primer "is not complementary to the first

strand cDNA nor the mRNA molecules initially present in the sample" (page 39, lines 13-15) and that the heel sequence of the second heeled primer "is not complementary to the mRNA molecules present in the sample or with the first strand cDNA molecules synthesized at step a)", thus the heel sequences are "unique"),

and either or each heel sequence includes a RNA polymerase promoter site (see for example page 39, lines 16-17 (for the "first heeled primer") and page 40, lines 29-31 (for the "second heeled primer"); note also Richardson's Example V uses a T7 RNA polymerase promoter sequence for the first primer (page 55, lines 24-33) and a T3 RNA polymerase promoter sequence for the second primer (page 56, lines 24-31)),

and the FAP includes a variable sequence (Richardson teaches each primer as having a variable sequence; see page 39, lines 19-22 (for the first heeled primer) and page 40, lines 20-22 (for the second heeled primer)),

whereby the RNA is reverse-transcribed to produce double-stranded cDNA and then multiple cDNAs according to the variable sequence (page 25, lines 32-33 and page 26, line 21 through page 28, line 2; page 39, lines 19-22; page 40, lines 20-22; it is clear that the products synthesized are determined in part by the variable sequences present in the heeled primers);

and (ii) of amplifying the cDNA using primers sufficiently complementary to the primer sequences FAP and TAP, within FAP-RAND and TAP-RT (26, lines 4-7; page 31, line 26 through page 32, line 2).

With regard to claim 2, Richardson teaches *in vitro* transcription (see page 37, lines 12-25 and page 38, lines 5-24, for example).

With regard to claim 3, Richardson's Example V uses a T7 RNA polymerase promoter sequence for the first primer (page 55, lines 24-33) and a T3 RNA polymerase promoter sequence for the second primer (page 56, lines 24-31).

With regard to claim 4, see page 38, lines 5-24. Richardson teaches incorporation of an RNA polymerase promoter in the [first heeled] primer allows synthesis of complementary RNA, whereas incorporation of an RNA polymerase promoter in the second heeled primer allows synthesis of sense RNA. Either of these embodiments generates a strand-specific library.

With regard to claim 5, Richardson teaches using the method for the production of a subtracted library (page 44, lines 6-17; the "two cell populations" is implied by the "two different samples" at line 13).

With regard to claim 6, Richardson teaches immobilizing the polynucleotide products of his method to an array (page 37, lines 23-25). Note that there is no explicit definition of "cloning" in Applicant's disclosure. Therefore, the generation of multiple copies of a particular polynucleotide, as in the method of Richardson, can be considered "cloning".

With regard to claim 8, Richardson teaches using a sample from patch clamp harvesting (page 59, lines 14-28).

With regard to claims 9 and 10, Richardson teaches the first and second heeled primers having cleavage sites at the 3' ends of the heel sequences (page 39, lines 28-31 and page 40, lines 23-26).

With regard to claim 11, Richardson teaches the cleavage sites in the first and second heeled primers are identical (page 42, lines 25-27).

With regard to claim 12, Richardson teaches the cleavage sites in the first and second heeled primers are identical (page 42, lines 28-30).

With regard to claim 13, Richardson teaches an embodiment which includes an additional step of treating the polynucleotides with an agent (restriction enzyme) that cleaves at the cleavage site (page 35, lines 29-34).

With regard to claim 14, Richardson teaches up to 50 amplification cycles (page 31, lines 13-15).

With regard to claim 15, Richardson teaches each amplification cycle comprises the steps of obtaining single-stranded DNA molecules at a temperature between 80°C and 95°C (which overlaps the claimed range; page 32, lines 5-6), annealing the single-stranded DNA molecules at a temperature between 65°C and 75°C (which overlaps the claimed range; page 32, lines 10-12), and elongating the annealed DNA molecules at a temperature between 65°C and 75°C (which encompasses the claimed range; page 32, lines 10-12).

With regard to claim 16, Richardson teaches each of these characteristics of the first heeled primer on page 39, lines 10-22:

In another aspect of the third embodiment of the present invention, the first heeled primer population consists of a population of nucleic acids comprising, from 5' end to 3' end:

(i) a heel sequence of 15 to 22 nucleotides in length which is not complementary to the first strand cDNA nor the mRNA molecules initially present in the sample;

(ii) An option but preferably present RNA polymerase promoter site;

(iii) an oligo dT sequence of 15 to 35 nucleotides in length; and

(iv) a variable sequence of 2-4 nucleotides in length that can hybridize to a mRNA molecule at the 5'end of the poly-A tail thereof, wherein substantially every possible variable sequence combination is found in said first heeled primer population.

With regard to claims 17 and 18, Richardson teaches detection of the sequence of interest according to the recited methods (page 5, lines 11-23):

Increase the number of nucleotide sequences corresponding to the mRNA species present in a sample is intended to designate an increase in nucleotide sequence to obtain a number of copies which is sufficient to allow at least one of the following methods:

(i) detection of the sequence of interest with specific oligonucleotide probes;

(ii) amplification of the sequence of interest with specific oligonucleotide primers;

(iii) cloning of the DNA molecules obtained in a replication and/or expression vector, or

(iv) In vitro RNA transcription, either for hybridization assays of for further reverse transcription optionally using unlabelled or labeled substrates followed by gene specific PCR or hybridization.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson et al (WO 01/06004 A2, cited on the IDS of 8/28/2006) in view of Fend et al (American Journal of Pathology, vol 154, no 1, pp 61-66, 1999).

The teachings of Richardson have been discussed. Richardson does not teach using a sample in his method that was obtained by laser capture microdissection.

Fend teaches a method for laser capture microdissection to obtain single cells for mRNA analysis (see entire article). Feng teaches that analysis of gene expression in normal or pathologically altered cells can "lead to the establishment of genetic fingerprints of neoplasms" (page 61, 1st paragraph following abstract). Feng also teaches that microdissected samples allows the isolation of morphologically identified cell populations down to the single-cell level, which overcomes the problem of tissue heterogeneity that can confound the attempt to differentiate gene expression patterns between neoplastic and non-neoplatic tissue (page 61, 1st and 2nd paragraphs following abstract).

It would have been *prima facie* obvious to use Richardson's methods to analyze samples obtained by laser capture microdissection, since Feng clearly teaches the value of laser capture microdissected samples and since Richardson was clearly interested in analyzing the RNA content of single cells (e.g. see page 3, lines 26-29, page 43, lines 32-35, page 44, lines 34-35, page 45, lines 1-3, page 58, lines 11-16). Thus it would have been obvious to one of skill in the art at the time the invention of the instant application that Richardson's method was ideally suited for the analysis of laser capture microdissection samples.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

scw

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